REMARKS

In reply to the Office Action dated December 23, 2005, claims 71-86 are currently under examination in the Application. By the above amendment, claim 71 has been amended to incorporate the limitation of claim 72, and claim 72 has been canceled. This amendment does not constitute new matter. The above amendment is not to be construed as acquiescence to the stated grounds for objection/rejection and is made without prejudice to prosecution of any subject matter modified and/or removed by this amendment in a related divisional, continuation and/or continuation-in-part application.

Rejections Under 35 U.S.C.§ 103, Webb and Mehlhorn

Claims 71-79 and 81-85 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Webb (5,741,516), alone or in combination with Mehlhorn (5,762,957), or vice versa (Mehlhorn in view of Webb). Specifically, the Examiner asserts that Webb teaches a method of preparing liposomes comprising vinca alkaloids, which includes the steps of: (1) preparing vinca alkaloid solution; (2) preparing liposomes comprising sphingomyelin and cholesterol with an acidic interior (citrate buffer); and (3) adding disodium hydrogen phosphate to the external medium to create a pH gradient with an external pH of 7.2 to 7.6, which facilitates loading of the vinca alkaloid solution into the liposomes. The Examiner concedes that Webb does not teach a kit comprising the various reagents used in this method of preparing liposomes comprising vinca alkaloids. Rather, the Examiner contends that the supply of reagents to prepare vincristine sulfate loaded in liposomes just before use by the method taught by Webb would have been obvious to one of ordinary skill in the art with a reasonable expectation of success. In addition, the Examiner asserts that Mehlhorn teaches a kit comprising reagents to prepare drug-loaded liposomes just prior to use, in order to prevent degradation of vesicles and leakage of drug, and concludes that it would have been obvious to one of ordinary skill in the art to supply the reagents of Webb in the form of a kit, since Mehlhorn teaches advantages of using kits to load liposomes with drug immediately prior to use. The Examiner also asserts that the use of vinca alkaloids as the chemical species in the kit of Mehlhorn would have been obvious, since Webb teaches a loading method that is the same as the one described in Mehlhorn, although he does concede that Mehlhorn does not itself teach the use of vinca alkaloids.

Applicants respectfully traverse this basis of rejection and submit that the claimed kits are not obvious in light of Webb or Mehlhorn, either alone or in combination. Applicants submit that in order to establish obviousness, the PTO must show: (1) the reference(s) teach or suggest all claim limitations; (2) the reference(s) provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) the combined teachings of the reference(s) indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. In the instant case, the Examiner has failed to meet these requirements. Comments specific to each combination of references are provided below.

1. Webb alone

Webb does not teach or suggest a kit comprising three separate vials containing components for use in preparing a liposomal vinca alkaloid formulation, as presently claimed. In contrast, Webb teaches a liposomal vinca alkaloid formulation having increased drug retention and enhanced stability (column 5, lines 31-38). Webb is silent regarding kits *per se*, but teaches that the drug-loaded liposomes may be prepared as pharmaceutical compositions (*e.g.*, with appropriate carriers and buffer and sterilization) and then "packaged for use or filtered under aseptic conditions and lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration" (column 8, lines 52-57). Clearly, these packaged pharmaceutical compositions comprise liposomes already loaded with drug, *e.g.*, vinca alkaloid, and are, therefore, not kits comprising separate vials of liposomes and drug suitable for loading by the user. Thus, Webb fails to teach or suggest each element of the claimed kits, and cannot, therefore, render them obvious.

Webb provides no teaching, suggestion, or motivation to modify the liposomal formulations or pharmaceutical compositions described by Webb to produce a kit comprising three distinct components, including: (1) a vinca alkaloid solution; (2) a solution of liposomes comprising sphingomyelin and cholesterol with an interior and exterior acidic pH; and (3) a buffer having a higher pH than the pH of the second vial, such that the combining this buffer with the solution of the second vial results in a neutral pH. Indeed, Webb provides absolutely no

motivation to produce a kit comprising vinca alkaloid and unloaded liposomes in separate vials, thereby requiring the user to prepare the loaded liposomes.

According to the teachings of Webb, the drug-loaded liposomes have increased drug retention and stability, and may be packaged or lyophilized and reconstituted with a sterile aqueous solution prior to administration, as described above. This is contrary to the idea of preparing drug-loaded liposomes from a kit immediately prior to use and therefore, provides no motivation for the skilled artisan to produce a presently claimed kit. Webb provides absolutely no suggestion to provide the drug separately from the liposomes, and the skilled artisan would clearly not be motivated to do so, given that Webb teaches that drug-loaded liposomes may be prepared in advance and stored prior to use. Clearly, it is simpler for users to merely reconstitute or use pre-loaded liposomes than to load the liposome themselves, with the associated risks of error and inconsistency.

Furthermore, with respect to vincristine, it was known prior to the filing of the instant application that vincristine is a relatively labile molecule with an optimal pH for stability of 3.5 to 5.5 (Vendrig *et al.*, *International Journal of Pharmaceutics*, 50:198-196 (1989)). Therefore, the liposomal vincristine formulations described by Webb, which have an acidic intraliposomal pH, would have been expected to provide a stable environment for vincristine. This is yet another reason why the skilled artisan would lack motivation based upon Webb to modify its teachings of pre-loaded liposomal formulations to remove the drug from the liposome and provide it in a separate container.

Applicants submit that Webb fails to describe each element of the claimed kits and provides no motivation to modify its teachings to produce the claimed kits. Accordingly, Webb fails to render the claimed kits obvious.

2. Webb in view of Mehlhorn

Webb in view of Mehlhorn fails to teach each element of the presently claimed kits. Specifically, neither Webb or Mehlhorn teach a kit comprising a vinca alkaloid in a separate container (*e.g.*, vial) from the liposomes and buffers used to adjust the final pH to the physiological range, as presently claimed.

As described in detail above, Webb clearly fails to describe a kit comprising three separate vials including: (1) a vinca alkaloid solution; (2) liposomes in solution, having an acidic intraliosomal and extraliposomal pH; and (3) a buffer having a higher pH, such that combining the solution of the second and third vial results in a physiological pH. Mehlhorn fails to remedy this deficiency, since it also does not describe a kit having these components.

Mehlhorn describes two kits: a two-component kit and a three-component kit. In the embodiment most relevant to the instant claims, the two-component kit includes: (1) a solution comprising empty liposomes in an acidic buffer; and (2) a solution comprising a basic buffer, wherein the drug is present in the solution that affords it the greatest chemical stability. Therefore, in the context of vincristine, which was known to be more stable in an acidic environment, the drug would be present in the solution containing the liposomes. This kit is clearly substantially different from the presently claimed kit, since it includes the drug in the same solution as either the liposomes or the buffer used to create the pH gradient, while the presently claimed kit provides the drug is a separate vial from either of these components.

In the embodiment described by Mehlhorn most relevant to the instant claims, the three-component kit includes: (1) a solution comprising empty liposomes in an acidic buffer; (2) a solution comprising a basic buffer; which when combined with the first solution results in a non-physiological pH; and (3) a solution comprising a buffer to adjust the pH of the combined first and second solutions to a physiological pH. The drug, when present, must be in the first or second solution, in order to achieve pH gradient-driven loading. This kit is also substantially different from the presently claimed kit. First, the second solution of the kit described by Mehlhorn has a pH such that when it is combined with the first liposome-containing solution, it produces a pH gradient having a non-physiological pH exterior of the liposomes. In contrast, the pH of the buffer solution of the presently claimed kit is such that it results in a physiological pH exterior of the liposomes when combined with the solution containing the liposomes. In addition, when present in the three component kit described by Mehlhorn, the drug is included in either the same vial as the liposomes or in the vial containing the buffer used to create the pH gradient. This is not the case in the presently claimed kits, where the drug is provided in a

separate vial. Accordingly, Mehlhorn fails to remedy the deficiencies of Webb, since together these two references fail to teach each element of the presently claimed kits.

The skilled artisan would not be motivated by Mehlhorn to modify the teachings of Webb to achieve the presently claimed kit. According to the Examiner, Mehlhorn would motivate the skilled artisan to modify the teachings of Webb to produce the presently claimed kit, since Mehlhorn teaches that kits for loading liposomes prior to use offer the advantages of reduced leakage of drug from vesicles and reduced degradation of vesicles prior to administration. However, these were not problems associated with the liposomal drug formulations described by Webb. As described in Webb, sphingomyelin-based liposomes have enhanced drug retention properties and stability as compared to other lipids conventionally used in liposomes. Thus, the skilled artisan would not be motivated by Mehlhorn's teachings related to drug leakage and liposome degradation to modify the liposomal drug formulations of Webb to create a kit of individual components, thus burdening the user with performing the drug loading procedure (see accompanying Declaration of Dr. Thomas D. Madden).

3. Mehlhorn in view of Webb

Mehlhorn, alone or in combination with Webb, fails to teach each element of the presently claimed kits. First, contrary to the Examiner's assertion, which provides a fundamental basis for the rejection based upon Mehlhorn in light of Webb, the loading method described by Mehlhorn is distinct from the loading method performed using the claimed kits. Specifically, the method described by Mehlhorn, and for which the kits described by Mehlhorn are adapted, involves preparing liposomes having a pH gradient across their membranes, wherein the pH of the solution exterior of the liposomes is not a physiologically benign pH. It is only upon addition of a further solution that the pH is adjusted to a physiologically benign pH. In contrast, the method of the present invention involves preparing liposomes having a pH gradient across their membranes, wherein the pH of the solution exterior of the liposomes is physiologically benign (neutral pH).

This difference in the method described by Mehlhorn is reflected in the specific components of the kits described by Mehlhorn, which include a solution that adjusts the pH of the solution exterior of the liposomes to a physiologically benign pH following loading. The

presence of such a solution is not required in the presently claimed kits. Accordingly, Applicants submit that it would not be obvious to use vinca alkaloids in the kit of Mehlhorn to achieve the presently claimed invention, since the kit of the presently claimed invention includes substantially different components, *e.g.*, "a third vial comprising a buffer solution having a pH higher than the pH of the solution of the second vial, such that combining the solutions of the second and third vials results in the pH of the exterior of said liposomes being neutral," which are not present in the kits described by Mehlhorn and are not obvious in light of the method described by Mehlhorn.

Mehlhorn, alone or in combination with Webb, provides no motivation to produce the presently claimed kits. The presently claimed kits include liposomes comprising sphingomyelin and cholesterol. The fact that these liposomes are associated with increased drug retention would suggest to the skilled artisan that the liposomal formulations described in Webb could be prepared and stored prior to use, as discussed in detail above. In contrast, Mehlhorn does not specifically describe the use of liposomes comprising sphingomyelin and cholesterol. Accordingly, while it may be advantageous to provide kits for preparing liposomal drug formulations using the liposomes exemplified in Webb, *e.g.*, phosphatidyl choline-based liposomes, this provides no basis or motivation to produce kits comprising liposomes prepared from sphingomyelin and cholesterol, as presently claimed. Rather, the skilled artisan, having knowledge from Webb of the enhanced drug retention properties of sphingomyelin and cholesterol-based liposomes, would not be motivated by Mehlhorn, which is directed to liposomes lacking this advantage, to produce the presently claimed kits (*see* accompanying Declaration of Dr. Thomas D. Madden). Accordingly, these references fail to provide the requisite motivation to combine to establish a case of obviousness.

Rejections Under 35 U.S.C.§ 103, Webb and Mehlhorn and Lenk

Claims 80 and 86 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Webb, alone or in combination with Mehlhorn, or *vice versa*, further in view of Lenk (5,762,957). The Examiner asserts that, in addition to the teachings of Webb and Mehlhorn described above, Lenk teaches the use of a cryoprotectant such as mannitol.

With regard to the various combinations of references including Lenk, Applicants submit that Lenk fails to remedy the deficiencies of Webb and Mehlhorn described above, and, therefore, the instant claims are not obvious in light of Webb, alone or in combination with Mehlhorn, further in combination with Lenk, for the same reasons detailed above with regard to claims 71-79 and 81-85.

In addition, Applicants further submit that Webb, alone or in combination with Mehlhorn, further in view of Lenk, fails to teach each element of the kit of claim 86, including the specific concentrations and pHs of the solutions present in the recited kit. Thus, Webb, alone or in combination with Mehlhorn, in view of Lenk, cannot render claim 86 obvious.

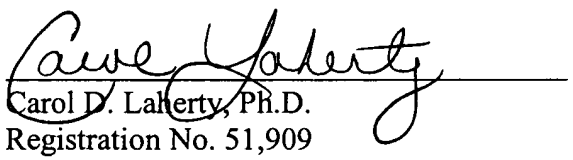
In light of the above amendment and remarks, Applicants respectfully request that the Examiner reconsider and withdraw these bases of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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Enclosure:
Declaration of Thomas D. Madden, Ph.D.

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